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(54) Title: GABA ANALOGS TO PREVENT AND TREAT GASTROINTESTINAL DAMAGE

(57) Abstract

GABA analogs are useful to prevent and treat gastrointestinal damage and ethanol withdrawal syndrome. Preferred treatments employ gabapentin or pregabalin.

GABA ANALOGS TO PREVENT AND TREAT GASTROINTESTINAL DAMAGE

FIELD OF THE INVENTION

This invention relates to a method for preventing visceral and gastrointestinal damage such as gastric ulcers by administering a gamma-aminobutyric acid (GABA) analog, and for treating gastrointestinal diseases such as inflammatory bowel disorders (IBD), functional bowel disorders (FBD), including dyspepsia and other visceral pain.

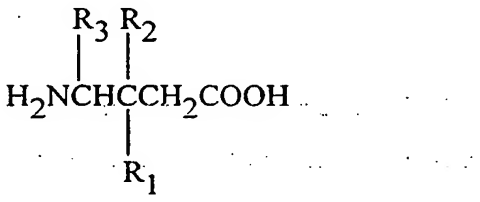
BACKGROUND OF THE INVENTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed drugs for the treatment of pain associated with osteoarthritis and many other musculoskeletal and inflammatory disorders. In the United States, about 100 million prescriptions are written each year to provide effective relief of pain and treatment of inflammatory diseases. Commonly used NSAIDs include sulindac, naproxen, indomethacin, mefenamic acid, diclofenac, fenoprofen, and diflunisal.

However, considerable evidence indicates that NSAIDs have frequent, serious, and costly gastrointestinal tract toxic side effects. These include mild dyspepsia, gastritis, peptic ulcer disease, as well as more serious gastrointestinal complications such as bleeding and perforation, leading sometimes to significant morbidity and, to a lesser extent, mortality. Serious GI complications due to NSAID use represent the greatest threat to life in patients with connective tissue diseases, second only to the primary disease and its complications. Similar gastrointestinal damage is caused by ingestion of alcohol. Indeed, a condition known as ethanol withdrawal syndrome is commonly encountered when prolonged ethanol consumption is terminated. In addition to gastrointestinal damage, this syndrome often results in tremors, anxiety, convulsions, hallucinations, and confusion.

wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof. An especially preferred embodiment utilizes a compound of Formula I where R_1 is hydrogen and n is 5, which compound is 1-(aminomethyl)-cyclohexane acetic acid, known generically as gabapentin. Other preferred GABA analogs have Formula I wherein the cyclic ring is substituted, for example with alkyl such as methyl or ethyl. Typical compounds include (1-aminomethyl-3-methylcyclohexyl)acetic acid, (1-aminomethyl-3-methylcyclopentyl)acetic acid, and (1-aminomethyl-3,4-dimethylcyclopentyl)acetic acid.

In another embodiment, the method of the invention utilizes a GABA analog of Formula II



II

or a pharmaceutically acceptable salt thereof, wherein

R_1 is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;

R_2 is hydrogen or methyl; and

R_3 is hydrogen, methyl, or carboxyl.

Diastereomers and enantiomers of compounds of Formula II can be utilized in the invention.

An especially preferred method of the invention employs a compound of Formula II where R_2 and R_3 are both hydrogen, and R_1 is $-(CH_2)_{0-2}$-i C_4H_9 as an (R), (S), or (R,S) isomer.

A more preferred embodiment of the invention utilizes 3-aminomethyl-5-methyl-hexanoic acid, and especially (S)-3-(aminomethyl)-5-methylhexanoic acid, now known generically as pregabalin, as well as CI-1008. Another preferred compound is 3-(1-aminoethyl)-5-methylhexanoic acid.

and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses. Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch, cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol, glycerin; sorbitol; polyethylene glycol; water; agar; alginic acid; isotonic saline, and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations. The compositions of the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents. For use in combating the gastrointestinal effects of NSAIDs, the GABA analogs can be administered alone in unit dosage form, or in combination with the NSAID being utilized for the particular patient.

The percentage of the active ingredient in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a concentration of at least 10% in a solid composition and at least 2% in a primary liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredient is present, for example, from 10% to 90% by weight.

Routes of administration of the subject compound or its salts are oral or parenteral. For example, a useful intravenous dose is between 5 and 50 mg and a useful oral dosage is between 20 and 800 mg. The dosage is within the dosing range used in treatment of gastrointestinal diseases such as ulcers and IBS, or as would be dictated by the needs of the patient as described by the physician.

A unit dosage form of the GABA analog to be used in this invention may also comprise other compounds useful in the therapy of gastrointestinal diseases.

The advantages of using the compounds of Formula I and II, especially gabapentin and pregabalin, in the instant invention include the relatively nontoxic nature of the compounds, the ease of preparation, the fact that the compounds are

Figure 3 shows the effect of gabapentin on memory and drowsiness in animals receiving chronic ethanol treatment.

Figure 4 shows the effects of gabapentin, CI-1008 (pregabalin), and morphine on colonic allodynia.

Figure 5 shows the effects of gabapentin and CI-1008 on colonic pain threshold in rats.

EXAMPLE 1

Gabapentin was evaluated in animals to determine its ability to prevent gastric lesions otherwise caused by indomethacin.

Male Sprague-Dawley rats weighing 240 to 250 g were fasted for 24 hours and allowed free access to water prior to experiment. All test drugs were given intragastrically. Rats were pretreated with different doses of gabapentin at doses of 40 and 60 mg. Thirty minutes later indomethacin (25 mg/kg) was administered. Another group of rats received 10 mg of gabapentin twice, 3 hours apart, followed by indomethacin administration. Three hours after indomethacin treatment, the rats were killed and gastric lesions were assessed. The severity of the lesions were determined by the measurement of the square area (mm^2) of visible lesions.

Results

1. Indomethacin caused severe gastric hemorrhagic injury; the areas of injury were measured at 42.6 ± 5.2 mm^2 (mean. ± standard error of mean).

2. Gabapentin pretreatment significantly reduced indomethacin-induced gastric injury. The gastric lesion with different doses of gabapentin pretreatment after indomethacin treatment were measured: 22.3 ± 2.8 mm^2 with 40 mg, 16.5 ± 2.2 mm^2 with 60 mg/kg, and 4.2 ± 0.39 mm^2 with 10 mg twice.

3. Gabapentin pretreatment also dramatically reduced gastric bleeding.

The foregoing data are presented in Figure 1, where the first bar is control (animals treated with indomethacin alone); Bar 2 is for animals treated with one

Administration of GABA Analogs and Ind methacin:

Gabapentin or pregabalin (CI-1008) were dissolved in water and administered orally at the following doses: 1, 10, 100, and 200 mg/kg in a volume of 1 mL. Control animals were dosed with an equal volume of vehicle (1 mL of water). Sixty minutes later, all the animals received 1 mL of a solution of indomethacin dissolved in 5% aqueous $NaHCO_3$ (80 mg/kg). Control animals received 1 mL of 5% aqueous $NaHCO_3$ orally. Experimental groups were as follows:

Group	Pretreatment	Damaging Agent
Group 1	Water	None ($NaHCO_3$)
Group 2	Water	Indomethacin 80 mg/kg
Group 3	Gabapentin 1 mg/kg	Indomethacin 80 mg/kg
Group 4	Gabapentin 10 mg/kg	Indomethacin 80 mg/kg
Group 5	Gabapentin 100 mg/kg	Indomethacin 80 mg/kg
Group 6	Gabapentin 200 mg/kg	Indomethacin 80 mg/kg
Group 7	Pregabalin 1 mg/kg	Indomethacin 80 mg/kg
Group 8	Pregabalin 10 mg/kg	Indomethacin 80 mg/kg
Group 9	Pregabalin 100 mg/kg	Indomethacin 80 mg/kg
Group 10	Pregabalin 200 mg/kg	Indomethacin 80 mg/kg

Evaluation of the Effect:

Gastric damage caused by indomethacin correlates with inhibition of the cyclooxygenase product prostaglandin E2 (PGE_2). Animals were sacrificed by decapitation 4 hours post-indomethacin administration. The stomach was removed and opened along the greater curvature and its image digitized and stored on an optical disk using a 486-based PC computer equipped with CUE3 system imaging analysis software (Olympus Corp., Marietta, Georgia, USA). Two 6-mm biopsies were taken from a constant region of the gastric mucosa located in each side of the glandular portion of the stomach, and their PGE_2 content was measured using a commercially available ELISA kit (Assay Designs Inc., Ann Arbor, Michigan, USA). The presence of gastric damage was determined using the retrieved

lesions, peptic ulcers, and even lower gastrointestinal bleeding, otherwise caused by consumption of alcohol or NSAIDs. The GABA analogs also treat the effects of alcohol withdrawal, which is a syndrome characterized by tremor, hallucinations, and confusion, and general gastrointestinal disorders such as IBD and IBS.

The following tests establish that GABA analogs are useful to treat ethanol withdrawal syndrome.

EXAMPLE 4

Male albino mice of the outbred TO strain (Bantin and Kingman, UK) were used in all studies. The weight ranged from 25 to 35 g, with no more than a 5 g range in any single experiment. The mice were housed, eight per cage, at 21°C ± 1°C, with 55 ± 10% relative humidity, and a 12-hour light/dark cycle with the light phase between 09:00 to 21:00. All mice received ad libitum access to tap water and standard laboratory chow (RM-1, Special Diet Services, UK) until their use in experiments or until their diet was replaced with a liquid diet.

Induction of Physical Dependence

Ethanol was administered in a liquid diet schedule. All mice received control diet for an initial 2-day period. Ethanol treated mice then received a diet containing 3.5% (v/v) ethanol/water for 2 days, followed by a diet containing 7% ethanol for a further 5 days. The average intake was 22 to 30 g/kg/day. Control groups were pair-fed a control diet, balanced isocalorifically to match the ethanol containing diet. There were no differences in the weights of the ethanol-treated and control mice at the end of the treatment periods. When mice were withdrawn from the ethanol (between 07:00 AM and 09:00 AM), they were provided with tap water until their use in experiments.

Drug Treatment

Gabapentin was dissolved in saline, the solution being made freshly each testing day. Intraperitoneal (i.p.) injections of either gabapentin, 10 mL/kg, or saline, were given immediately on withdrawal from the ethanol treatment in the studies on the handling responses, and 2 hours prior to measurement of audiogenic

Elicitation of Audiogenic Seizures

At 8 and 12 hours from ethanol withdrawal, the susceptibility to sound-induced convulsions was measured in separate groups of ten mice. Mice were tested individually in a sound-proof perspex box 30 × 30 × 30 cm containing an electric door-bell. The bell was rung for 2 minutes or until the first signs of convulsions. The number of mice which responded by wild-running and clonic convulsions was counted. The mice were humanely killed as soon as a full convulsion was seen.

Anxiety-Related Behavior

Mice were withdrawn from the ethanol diet at 7:00 AM and tested for anxiety-related behavior 8 hours later using a murine elevated plus-maze. It was constructed of perspex with two opposing open arms (30 × 5 × 0.25 cm) and two opposing closed arms (30 × 5 × 15 cm) which extended from a central platform (5 × 5 cm). The floor was of matt black perspex. The animals were acclimatized to the experimental room 1 hour prior to experimentation. Experiments were conducted under dim red light, and each 5 minute session was video-taped for later analysis, by an observer unaware of the prior treatment. During this analysis (Observer 3.0, Noldus Information Technology, Wageningen, Netherlands) measurements were made of the time spent on each arm of the maze, the number of entries onto each arm and rearing activity. The measurements were made in accordance with the definitions in Table 3.

TABLE 3

Measurements of Behavior on the Elevated Plus Maze

- Arm entry = All four paws onto either a closed or an open arm.
- "Head Dip" = An exploratory forward head/shoulder movement over the side of an open arm and down towards the floor.
- "Protected head dips" = Exploratory forward head/shoulder movement over the side of a closed arm and down towards the floor.
- "Stretch-attend posture" = An exploratory flat body posture where the mouse stretches forward and then retracts to original position without moving forward.

RESULTS

Handling Response

The ratings of behavior in response to gentle handling showed the expected increase following withdrawal from the ethanol treatment. Gabapentin (GP), at 100 mg/kg (Figure 2a), significantly reduced this increase in ratings when the results were compared over the 12-hour testing period ($p < 0.001$). The effect of this dose of gabapentin showed a marked reduction in handling scores for around 4 hours. This time period was therefore used in later analysis to examine the area under the handling curve with each dose of the drug. The effects of lower doses of gabapentin were not significant over the 12-hour period of measurement, but when the areas under the curve were calculated for the first 4 hours of the study (Figure 2b), significant effects of the 20- and 50-mg/kg doses were seen ($p < 0.05$), as well as the 100-mg/kg dose ($p < 0.01$).

Audiogenic Seizures

At the 8-hour time interval, 50 and 100 mg/kg gabapentin decreased the convulsion incidence after the audiogenic stimulus, with the 100-mg/kg dose reaching statistical significance ($p < 0.05$). There was no effect of the lower doses (Table 4). No effect was seen of any of the doses tested at 12 hours from the end of the ethanol treatment (data not shown).

TABLE 4

The Effect of Gabapentin on Audiogenic Convulsions Measured 8 Hours From Ethanol Withdrawal

Chronic Treatment	Acute Injection	Percentage of Group Showing Clonic Convulsions
Control Diet	Saline	0
Ethanol Diet	Saline	80* $p < 0.05$ c.f. Control/Saline group
Ethanol Diet	Gabapentin 5 mg/kg	92
Ethanol Diet	Gabapentin 20 mg/kg	70
Ethanol Diet	Gabapentin 50 mg/kg	40
Ethanol Diet	Gabapentin 100 mg/kg	30 $p < 0.01$ c.f. Ethanol/Saline group

bilaterally in the abdominal external oblique musculature just superior to the inguinal ligament. Electrodes were exteriorized on the back of the neck and protected by a glass tube attached to the skin. Animals were individually housed in polypropylene cages and kept in a temperature-controlled room (21°C). They were allowed free access to water and food (UAR pellets, Epinay, France).

Electromyographic Recording

Electromyographic recording began 5 days after surgery. The electrical activity of abdominal striated muscles was recorded with an electroencephalograph machine (Mini VIII, Alvar, Paris, France) using a short-time constant (0.03 sec) to remove low-frequency signals (<3 Hz) and a paper speed of 3.6 cm/minute.

Balloon Distension Procedure

Rats were placed in plastic tunnels (6 cm diameter; 25 cm length) where they could not move, escape or turn around, in order to prevent damage to the balloon. They are accustomized to this procedure for 3 or 4 days before rectal distension (RD) in order to minimize stress reaction during experiments. The animals were determined to be accustomed to the plastic tunnel using two criteria: (i) a behavioral component: when the animals tried to escape or turn around no more than one time per 5 minutes, (ii) the abdominal basal activity: when abdominal striated muscles exhibited less than five abdominal contractions per 5 minutes in the absence of distension. The balloon used for distension was an arterial embolectomy catheter (Fogarty, Edwards Laboratories, Inc., Santa Ana, USA). Rectal distension (RD) was performed by insertion of the balloon (2-mm diameter; 2-cm long) in the rectum, at 1 cm of the anus, the catheter being fixed at the tail. It was inflated progressively by steps of 0.4 mL, from 0 to 1.6 mL, each step of inflation lasting 5 minutes. To detect possible leakage, the volume of water introduced in the balloon was checked by complete removal with a syringe at the end of the distension period.

TABLE 5

Effect of Gabapentin on Abdominal Response Induced by Rectal Distension (Number of abdominal contractions/5 minutes; mean ± SEM, n = 7-8, *p <0.05, **p <0.01, significantly different from vehicle; n% of reduction vs vehicle)

Volume of Distension	Vehicle (0.3 mL/rat)	Gabapentin (30 mg/kg)	Vehicle (0.3 mL/rat)	Gabapentin (100 mg/kg)
0.4 mL	4.4 ± 1.6	5.0 ± 2.1	3.9 ± 1.8	2.0 ± 1.4
0.8 mL	19.1 ± 2.8	10.6 ± 3.4** (-45%)	19.6 ± 2.3	7.6 ± 3.4** (-61.2%)
1.2 mL	23.4 ± 2.6	16.1 ± 2.3* (-31.2%)	19.1 ± 2.3	16.7 ± 2.9

TABLE 6

Effect of Gabapentin on LPS-Induced Delayed (12 Hours) Allodynia (Number of abdominal contractions/5 minutes; mean, ± SEM, n = 7-8, + p <0.001, significantly different from "LPS/vehicle" value; n% of reduction vs "LPS/vehicle")

Volume of Distension	LPS (1 mg/kg) + Vehicle (0.3 mL/rat)	LPS (1 mg/kg) + Gabapentin (3.0 mg/kg)
0.4 mL	9.7 ± 1.0	0.7 ± 0.5+ (-92.8%)
0.8 mL	11.7 ± 1.2	11.9 ± 0.8
1.2 mL	23.5 ± 2.2	16.3 ± 3.2

The foregoing experiment was carried out with the GABA-analog pregabalin. Pregabalin, at 30 mg/kg, reduced the number of cramps at both distension volumes of 0.4 and 0.8 mL. When injected 120 minutes before rectal distension, pregabalin, at both 10 and 30 mg/kg, had a similar effect at all distension volumes. LPS enhanced the number of abdominal contractions at the volume of 0.4 mL (9.7 ± 1.0 vs. 3.7 ± 1.0) 12 hours after its administration. This effect was suppressed when animals received pregabalin (1.8 ± 0.9 vs. 9.7 ± 1.0) at 30 mg/kg 30 minutes prior to rectal distension. These results establish that

In a third series, a group of eight rats treated with TNBS received a subcutaneous (sc) injection of gabapentin or CI-1008 30 minutes prior to initiation of the colonic distension cycle.

All test compounds were dissolved in saline except TNBS. TNBS was dissolved in EtOH 30% (w/v). Subcutaneous injection of vehicle was given in a volume of 2 mg/kg.

Statistical significance between each group was determined using a one-way ANOVA followed by Student's unpaired t-test. Differences were considered statistically significant at $p < 0.05$.

Pain threshold (pressure of distension inducing the first abdominal contraction) after distal colonic distension was determined at Day 7 in two groups of awake rats: control animals and TNBS-treated animals. A significant decrease in the pain threshold was observed in TNBS-treated animals. Inflammatory parameters (colon weight, area of hyperemia and necrosis and colonic myeloperoxidase content) were measured in the proximal colon at Day 7 after TNBS treatment. All the parameters were significantly increased except the area of necrosis.

Gabapentin (100, 300, and 500 mg/kg sc) and CI-1008 (30, 60, 100, and 200 mg/kg sc) were administered 30 minutes before colonic distension and measurement of the inflammatory parameters. Gabapentin inhibited in a dose-related manner the TNBS-induced colonic allodynia. At 500 mg/kg sc, gabapentin completely blocked the effect of TNBS on colonic pain. CI-1008 also showed a dose-related inhibition of the decrease in pain threshold. At 100 mg/kg, CI-1008 completely suppressed the allodynia induced by TNBS. Morphine (0.1 mg/kg sc) completely suppressed the TNBS-induced decrease in pain threshold after colonic distension (Figure 4). In contrast, neither gabapentin nor CI-1008 inhibited the colonic inflammatory effect of TNBS in these experimental conditions.

In normal conditions (control animals), morphine (0.3 mg/kg sc) significantly increased the colonic pain threshold while, in the same conditions, neither gabapentin (500 mg/kg sc) nor CI-1008 (200 mg/kg sc) modified the colonic pain threshold (Figure 5). The results are further shown in Tables 7 and 8.

TABLE 8

Effect of CI-1008 and Gabapentin on Colonic Threshold in Normal Rats

Treatment	Colonic Threshold (mm Hg)		SEM	n	p
Control	43.33	±	1.23	6	
CI-1008 200 mg/kg sc	46.41	±	2.26	8	NS
Gabapentin 500 mg/kg sc	43.75	±	1.44	6	NS

NS = Not significant vs control.

The foregoing data establish that GABA analogs such as gabapentin and CI-1008 suppress TNBS-induced colonic allodynia, and are therefore effective in abnormal colonic hypersensitivity reflecting the chronic pain in IBS.

EXAMPLE 7

Formalin-Induced Inflammatory Colonic Pain

The GABA analogs were evaluated in another model to determine their effect on inflammatory visceral pain, including pancreatitis and intestinal cystitis.

Administration of formalin into the wall of the rat colon causes acute inflammation and visceral pain. The aim of this study was to evaluate the antinociceptive activity of gabapentin and CI-1008 in visceral pain induced by colonic intrapariental injection of formalin.

Adult female Sprague-Dawley rats weighing 240 to 260 g were used in the study. The animals were housed three per cage in a regulated environment (20 ± 1°C, 50 ± 5% humidity, with light 8:00 AM to 8:00 PM) prior to use in the test.

Each test animal was placed in a transparent plastic cage (27 × 43 × 28 cm) with a layer of wood shavings on the floor. Drinking water was available. Cages were placed in such a way that visual interaction between animals was avoided. A mirror was positioned behind each cage to improve the recording of behaviors.

Statistical significance between each group was determined by using a one-way ANOVA followed by Student's unpaired t-test. Differences were considered statistically significant at $p < 0.05$.

Hyperalgesia is induced by intramural injection of formalin (5%, 50 µL/rat) into the colonic wall in unfasted female Sprague-Dawley rats. Gabapentin and CI-1008 were tested at 100, 300, 500 and 100, 200 mg/kg sc, respectively. Gabapentin and CI-1008 significantly and dose-dependently decreased the pain score induced by intracolonic formalin. The maximal inhibitory effect was observed after 500 mg/kg of gabapentin and 200 mg/kg of CI-1008. The results are presented in Table 9.

This study establishes that GABA analogs exhibit an antinociceptive effect on intra-colonic formalin-induced pain, and thus are effective in treating IBD and IBS, and visceral pain, including pancreatitis and intestinal cystitis.

TABLE 9

Effect of Subcutaneous Injection of Gabapentin and CI-1008 on Inflammatory Colonic Pain Induced by Intramural Injection of Formalin 5%

Treatment	% Antinociception		SEM	n	p
CI-1008					
100 mg/kg sc	18.55	±	7.41	7	***
200 mg/kg sc	70.81	±	7.47	6	***
Gabapentin					
0.3 mg/kg sc	-7.73	±	10.43	3	NS
100 mg/kg sc	13.62	±	12.65	9	NS
300 mg/kg sc	55.07	±	9.98	6	***
500 mg/kg sc	88.01	±	16.96	6	***

*** =

NS = Not significant vs control.

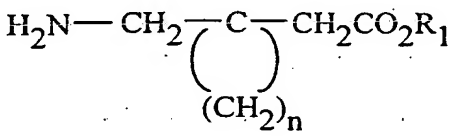
The following examples further illustrate compositions provided by the invention which contain a GABA analog in combination with an NSAID.

CLAIMS

What is claimed is:

1. A method for preventing and treating gastrointestinal damage and disorders comprising administering to a subject in need of treatment an effective amount of a GABA analog.

2. A method according to Claim 1 employing a compound of Formula I



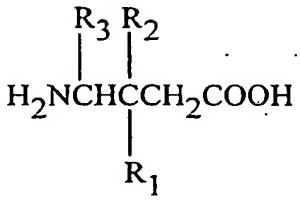
I

wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof.

3. The method according to Claim 2 employing gabapentin.

4. The method according to Claim 1 employing a compound selected from (1-aminomethyl-3-methylcyclohexyl)acetic acid, (1-aminomethyl-3-methylcyclopentyl)acetic acid, and (1-aminomethyl-3,4-dimethylcyclopentyl)acetic acid.

5. A method according to Claim 1 employing a compound of Formula II

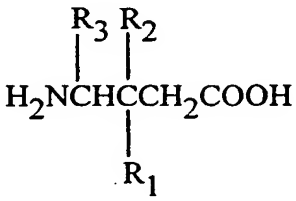


II

wherein R_1 is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;

14. The method according to Claim 13 employing gabapentin.

15. A method according to Claim 12 employing a compound of Formula II



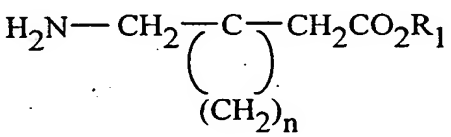
II

wherein R_1 is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;
R_2 is hydrogen or methyl; and
R_3 is hydrogen, methyl, or carboxyl, and the pharmaceutically acceptable salts thereof.

16. The method according to Claim 15 employing pregabalin.

17. A pharmaceutical composition comprising a GABA analog and a non-steroidal anti-inflammatory drug together with a pharmaceutically acceptable excipient, carrier, or diluent therefor.

18. A composition of Claim 17 wherein the GABA-analog is a compound of Formula I

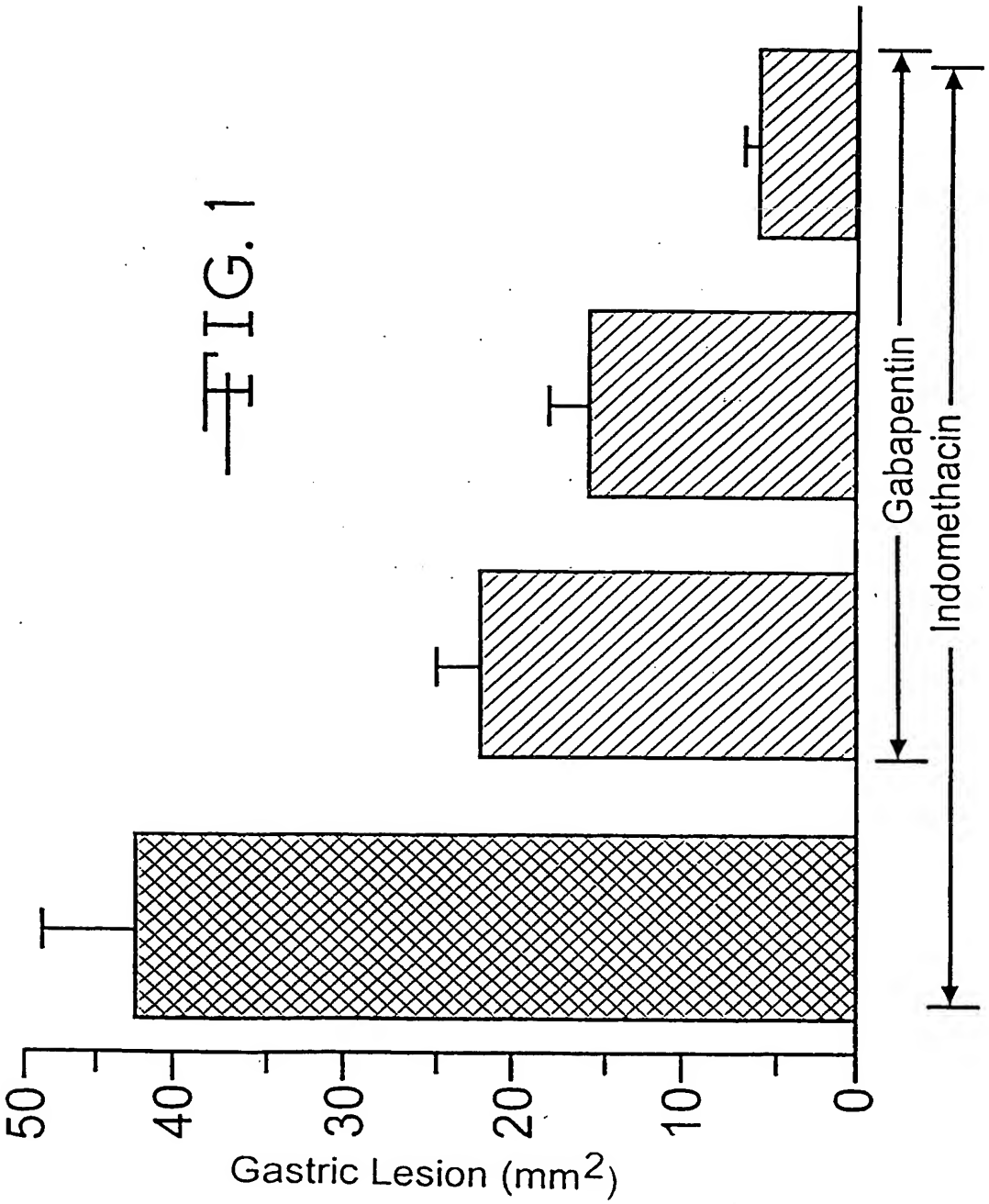


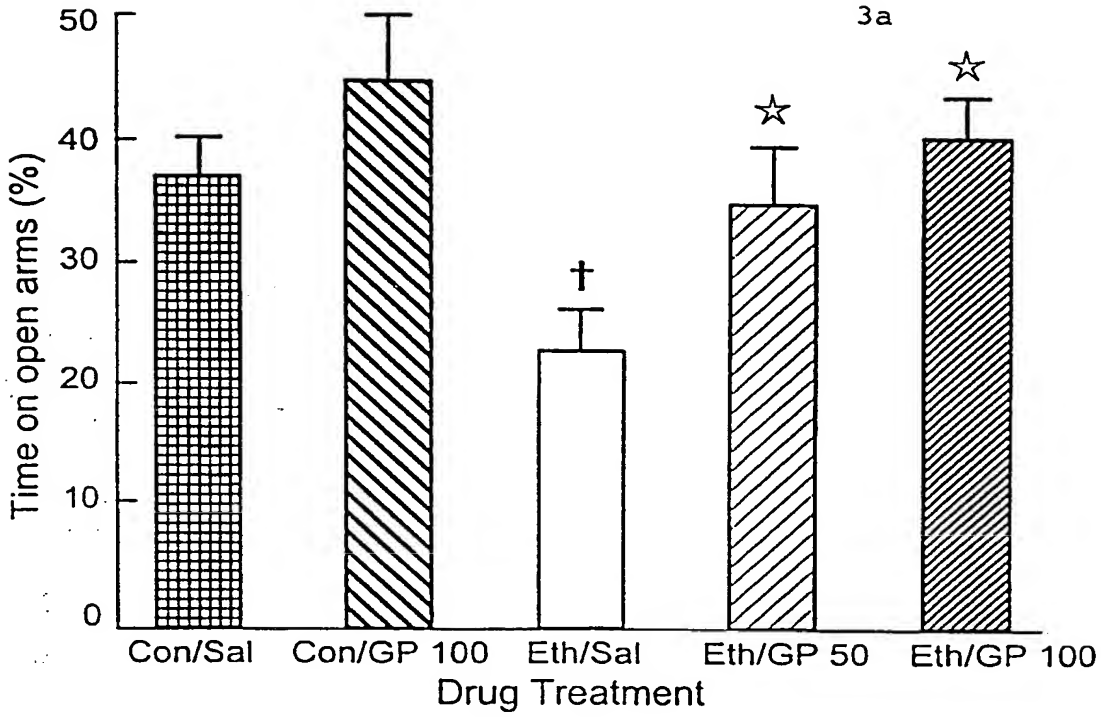
I

wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof.

19. The composition of Claim 18 wherein the GABA analog is gabapentin.

FIG. 1




3a
Time on open arms (%)
50
40
30
20
10
0
†
☆
☆
Con/Sal
Con/GP 100
Eth/Sal
Eth/GP 50
Eth/GP 100
Drug Treatment

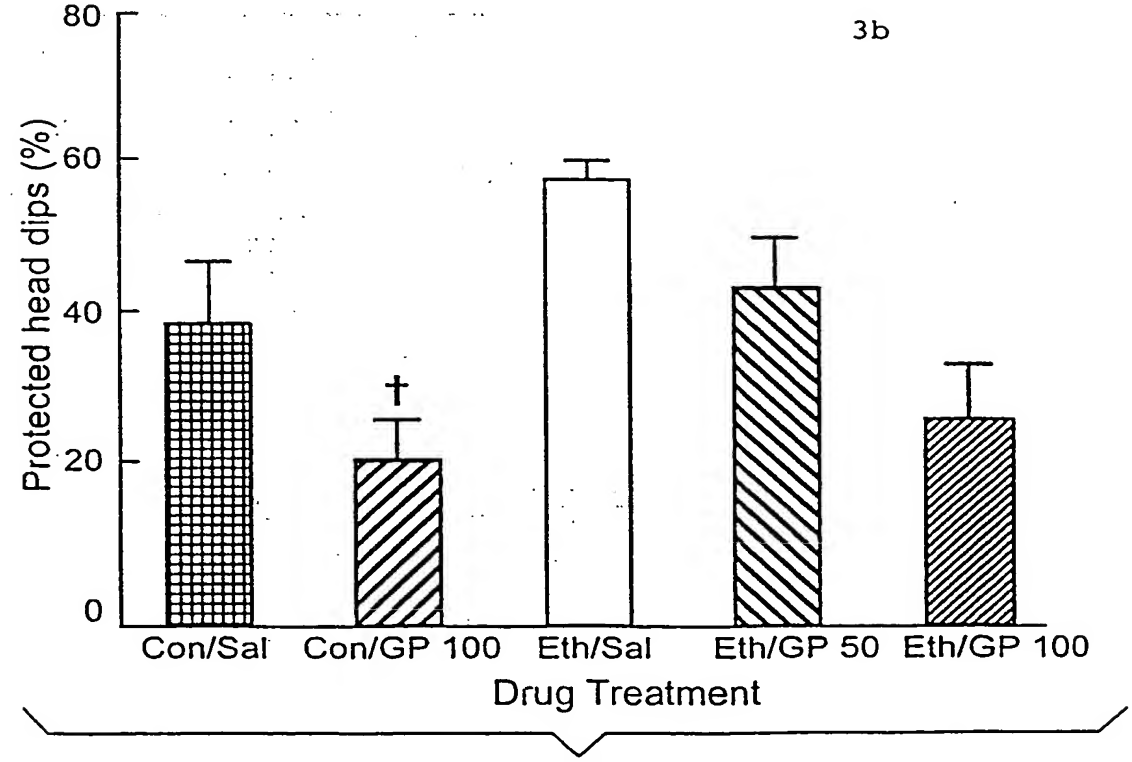

3b
Protected head dips (%)
80
60
40
20
0
†
Con/Sal
Con/GP 100
Eth/Sal
Eth/GP 50
Eth/GP 100
Drug Treatment

FIG. 3

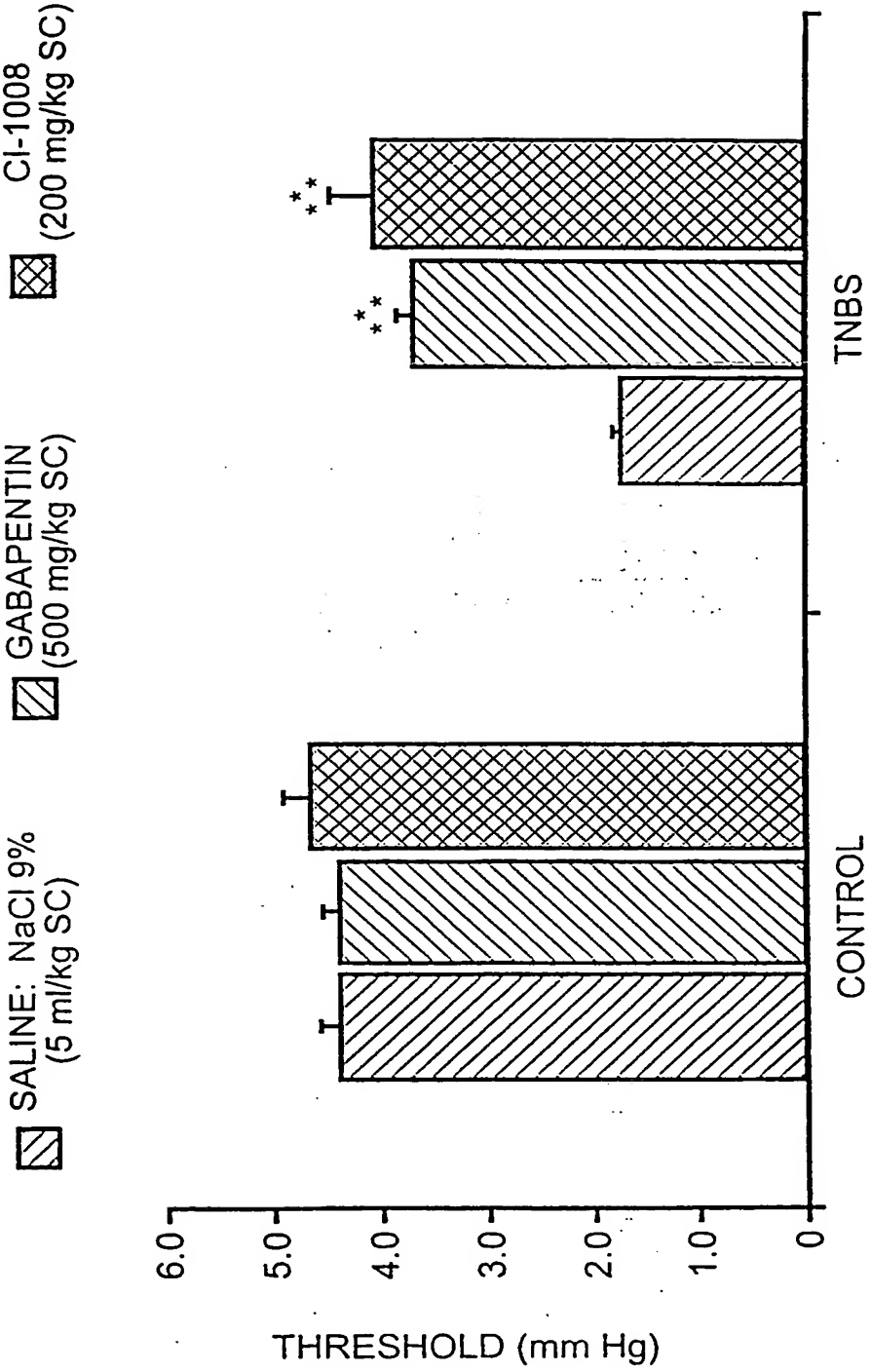

SALINE: NaCl 9% (5 ml/kg SC)
GABAPENTIN (500 mg/kg SC)
CI-1008 (200 mg/kg SC)
CONTROL
TNBS
THRESHOLD (mm Hg)
6.0
5.0
4.0
3.0
2.0
1.0
0

FIG. 5

INTERNATIONAL SEARCH REPORT

Intern. ial Application No
PCT/US 98/15694

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication,where appropnate, of the relevant passages	Relevant to claim No.
X,P	LESCH ET AL: "the gaba-derivative 3-isobutyl gaba acts centrally to protect against indomethacin-induced gastric damage in rats" GASTROENTEROLOGY, vol. 114, no. 4, 15 April 1998, page 200 XP002081396 see abstract ---	1,5-7,9, 12, 15-17, 20-23
X,P	REN ET AL: "effects of gabapentin on indomethacin-induced and ethanol-induced gastric injury" GASTROENTEROLOGY, vol. 114, no. 4, 15 April 1998, page 267 XP002081397 see abstract -----	1-3,9, 12-14, 17-19, 22,23

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna l Application No
PCT/US 98/15694

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9811885 A	26-03-1998	AU 4406497 A	14-04-1998
WO 9817627 A	30-04-1998	AU 4669797 A	15-05-1998
WO 9611680 A	25-04-1996	AU 3745895 A	06-05-1996